

MINIREVIEW

Effects of Antibiotics on Nosocomial Epidemiology of Vancomycin-Resistant Enterococci

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Enterococci are gram-positive cocci that are normal inhabitants of the gastrointestinal tract. However, they can also be significant pathogens, causing endocarditis and urinary tract, bloodstream, and wound infection (62). During the last decade, a dramatic increase in the occurrence of vancomycin-resistant enterococci (VRE) has been noted in hospitals within the United Kingdom and the United States (16, 87). For instance, a 9-year study from the United Kingdom determined that vancomycin resistance in *Enterococcus faecium* isolated in blood cultures reached 6.3% in 1993, 20% in 1995, and 24% in 1998 (87). According to the Centers for Disease Control and Prevention, the percentage of enterococcal isolates that were resistant to vancomycin reported by U.S. intensive care units (ICUs) increased from 0.3% in 1989 to 25.2% in 1999 (16). In a recently published international survey (57), the proportion of nosocomial enterococcal isolates in the United States that were resistant to vancomycin (17% in 1999) was much higher than the proportion of vancomycin-resistant enterococcal isolates from patients in the rest of the world (Fig. 1).

Since de novo emergence of glycopeptide resistance in enterococci through genetic mutations induced by glycopeptide exposure in an individual patient is unlikely (70), the inexorable increase in the prevalence of VRE in U.S. hospitals during the last decade was accelerated by cross-transmission via the hands of health care workers, contaminated equipment, and environmental surfaces (32, 55, 65, 73). Therefore, the presence of VRE within a hospital environment raises important issues in order to prevent the spread of VRE (65). First, improved hand hygiene practices and reliable cleaning techniques are warranted to decrease the spread of VRE (42). Second, the fact that many seriously ill patients may be asymptotically colonized requires screening policies for early detection and special isolation precautions for patients carrying VRE (8, 78). Finally, excessive antibiotic usage has been identified as one of the most important modifiable risk factors for VRE occurrence within the hospital setting (70).

Although the role of antibiotics in the nosocomial epidemiology of VRE has been extensively studied, many controversies remain. Therefore, we systematically reviewed the effect of

antibiotics on the nosocomial epidemiology of VRE. Specifically, we attempted to assess the effect of antibiotic exposure in two different patient populations: (i) VRE-negative patients (the risk of VRE acquisition was assessed in individual patients initially free of VRE) and (ii) patients already colonized with VRE. For the latter group of patients, the following qualities were assessed: (i) likelihood of detection of VRE, (ii) potential for VRE transmission, and (iii) chances of intestinal decolonization of VRE. In addition, we examined intervention studies that tried to modify antibiotic treatment protocols in order to decrease VRE prevalence. Finally, we evaluated potential limitations and biases on the validity of the reported results.

A literature search to identify all studies published between January 1980 and February 2001 that examined the role of antibiotic exposure in nosocomial VRE epidemiology was performed using the MEDLINE database and bibliographic review of relevant papers. Articles written in English, French, or German were considered for review. A full text search was performed using the index terms “vancomycin” and “enterococci” in different variations. All articles were considered, including reviews, editorials, book chapters, and clinical studies. We screened studies of hospitalized pediatric and adult patients that evaluated the effect of antibiotic exposure on nosocomial VRE detection, de novo acquisition, transmissibility, and decolonization. All studies reporting the effect of antibiotics on the outcome of interest were considered. Studies were excluded if they did not give any estimates about the effect of antibiotic exposure on nosocomial VRE epidemiology. In addition, we assessed animal or volunteer studies, if they were relevant for the purpose of this review. The decision to include or to exclude an article and the data extraction were accomplished independently by at least two reviewers using a computerized standard form. Disagreement was resolved by consensus. We abstracted the following data for each included study: year of publication, authors, setting, study period, type of study, sample size, exposures and outcomes of interest, inclusion criteria of the study subjects, and pattern of antibiotic exposure. References of all identified publications were entered into a database using reference-managing software (Endnote 4.0; Niles Software, Inc., Berkeley, Calif.).

We identified 1,761 potentially relevant articles from the literature search; 120 studies were selected, of which 113 were found to be suitable for this literature review.

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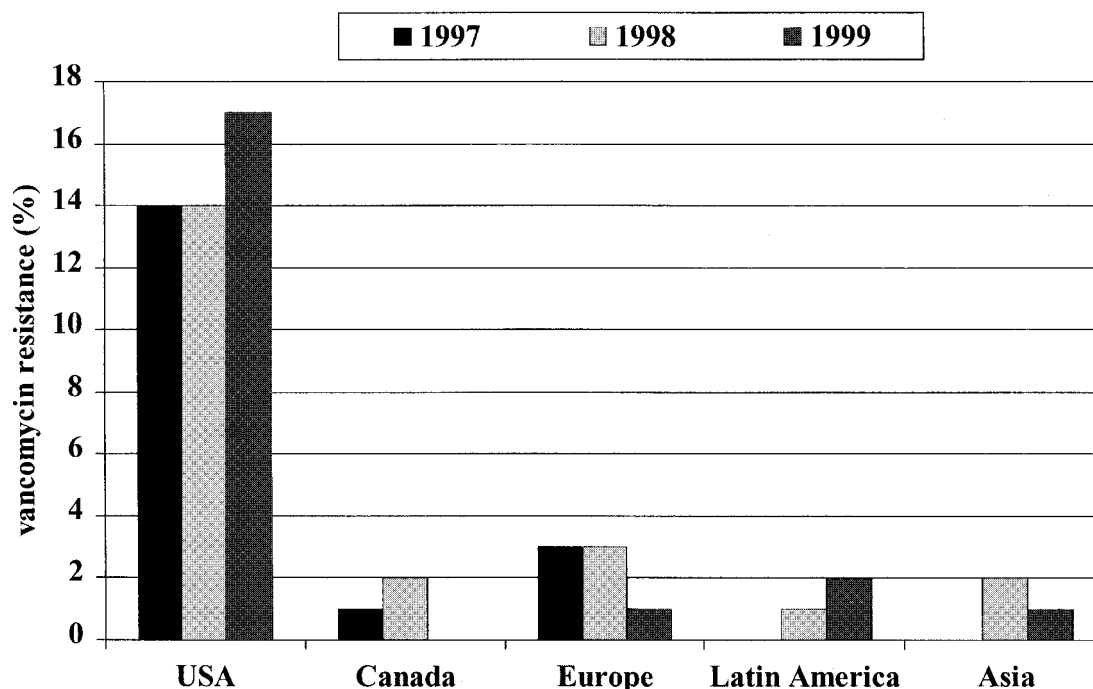


FIG. 1. Trends in vancomycin resistance of all tested enterococci ($n \approx 5,000$ nosocomial isolates) in each monitored region of the world, as reported by the SENTRY antimicrobial surveillance program (57).

CLINICAL STUDIES EVALUATING THE ROLE OF ANTIBIOTICS IN VRE ACQUISITION

VRE colonization and infection occur predominantly in patients with severe underlying disease, extended length of hospital stay, and previous antibiotic exposure (70). The most consistently recognized antibiotic agents inducing or facilitating the acquisition of VRE colonization or infection are vancomycin, cephalosporins, and antianaerobic agents. Moreover, the total volume of antibiotic agents and the duration of antibiotic treatment or prophylaxis seem to be important risk factors for the acquisition of VRE (40, 96, 97).

Vancomycin. Although the association between antecedent vancomycin treatment and VRE has been investigated in numerous studies, the true effect of oral or intravenous vancomycin exposure on the acquisition of VRE remains controversial.

While few clinical studies delineate the role of oral vancomycin in VRE acquisition, oral vancomycin use probably exercised some initial selection pressure, contributing to the emergence of this type of resistance. Indeed, one of the first documented cases of VRE was described in a patient who received oral vancomycin (54). As discussed later in this article, experimental data show that oral vancomycin use may promote overgrowth of VRE in mice and humans. Fortunately, this type of vancomycin use has almost been abandoned during the last decade after implementation of new guidelines for the treatment of *Clostridium difficile* colitis, and, therefore, epidemiologic data about the association of oral vancomycin use and VRE acquisition remain sparse.

In contrast, many reports describe an association between prior intravenous vancomycin use and VRE colonization or

infection (4, 11, 20, 53, 68, 72, 77, 80, 82, 86, 89–91, 96), whereas others found no such effect (8, 22, 28, 31, 35, 61, 78, 79, 83, 27, 98, 99, 106). A recent meta-analysis from Carmeli et al. (15) analyzed 20 epidemiologic studies and showed in a crude analysis that vancomycin exposure conferred a 4.5-fold increased risk of VRE acquisition (95% confidence interval [CI], 3.0 to 6.9). Those studies that used patients with vancomycin-susceptible enterococci as controls found a stronger association (pooled odds ratio [OR], 10.7; 95% CI, 4.8 to 23.8) than those that used controls from whom no VRE was isolated (pooled OR, 2.7; 95% CI, 2.0 to 3.8). Studies that were designed according to good epidemiological standards (41) and adjusted for length of stay (LOS) found only a small and nonsignificant association between vancomycin treatment and VRE acquisition (pooled OR, 1.4; 95% CI, 0.7 to 2.6). These investigators also detected publication bias, favoring reports that found a large measure of association. They concluded that the strong association between vancomycin treatment and hospital-acquired VRE that has been reported in the current literature may be due to flaws in the selection of the control group, confounding by duration of hospitalization, and publication bias. Studies that accounted for these factors found only a small and nonsignificant association. Likewise, Ostrowsky et al. (79) found after multivariable modeling that the only antibiotic exposure associated with VRE colonization at the time of admission to the ICU was broad-spectrum cephalosporin treatment, whereas vancomycin exposure was not a significant predictor of VRE colonization. These authors demonstrated the important confounding effect of LOS on the association between vancomycin and VRE, owing to the strong correlation between LOS and VRE colonization and between LOS and

vancomycin use. In contrast, adjustment for LOS attenuated the association between VRE colonization and broad-spectrum cephalosporins to a much lesser degree (79). Finally, a recently published study (78) reporting the control of a VRE outbreak in the Siouland region (Iowa, Nebraska, and South Dakota) revealed that none of the VRE-positive patients had received vancomycin within the previous 6 months, whereas exposure to a broad-spectrum cephalosporin was a strong risk factor for VRE colonization (OR, 14.1; 95% CI, 3.1 to 63.8).

Extended-spectrum cephalosporins. Other studies confirmed the importance of previous extended-spectrum cephalosporin treatment in the risk of VRE acquisition (4, 8, 21, 56, 64, 67–69, 75, 84, 91). Bonten et al. studied 13 ventilated patients who acquired VRE and 25 who did not, and observed that broad-spectrum cephalosporin use predicted acquisition, whereas vancomycin use was not a significant predictor (8). More recently, D'Agata et al. (20) showed that treatment with broad-spectrum cephalosporins predicted VRE acquisition among hemodialysis patients. A 52-week surveillance study of patients with hematologic malignancies substantiated the observation of an association between colonization with antibiotic-resistant *E. faecium* and treatment with broad-spectrum cephalosporins, which preceded the intestinal overgrowth with *E. faecium* in 93% of the patients (95).

In a meta-analysis examining the association between antecedent antibiotic exposure and VRE colonization or infection (S. Cosgrove, S. Harbarth, and Y. Carmeli, Abstr. 12th Annu. Sci. SHEA Meet., abstr. 72, 2002), we identified 19 studies that evaluated the effect of exposure to broad-spectrum cephalosporins (6–8, 20, 32, 38, 43, 45, 58, 68, 79, 82, 86, 91, 92, 93, 96–98). This analysis revealed a significant association between receiving broad-spectrum cephalosporins and VRE colonization or infection, with a pooled OR of 3.44 (95% CI, 2.36 to 5.0; $P < 0.001$).

Antianaerobic agents. Previous studies have also implicated prior exposure to antibiotics with activity against anaerobe microorganisms as an independent risk factor for colonization with VRE (4, 24, 58, 68, 81, 90, 96). However, methods of classifying antianaerobic agents differed between those studies. In their recently published study, Donskey et al. (24) demonstrated that treatment with antianaerobic antibiotics promoted high-density stool colonization with VRE. However, this prospective study examined principally patients already colonized with VRE, and, therefore, the study findings may not be entirely applicable to the initial acquisition of VRE colonization. Moreover, both vancomycin and ceftriaxone were classified as antianaerobic agents, in contrast to the usual method of classification. Interestingly, this study also incriminated several agents (e.g., imipenem and piperacillin-tazobactam) with both antienterococcal and potent antianaerobic activity, which have rarely been identified as important risk factors for VRE colonization. One possible explanation for this phenomenon may be strain differences (108). For instance, Pegues et al. (81) have shown by multivariate analysis that acquisition of a certain epidemic VRE strain was associated with prior receipt of clindamycin (OR, 10.5; 95% CI, 1.1 to 97.5) in that hospital.

In the aforementioned meta-analysis (Cosgrove et al., 12th Annu. Sci. SHEA Meet.), an evaluation of 14 studies that examined the relation between exposure to highly active antianaerobic agents (e.g., metronidazole and clindamycin) and

VRE colonization or infection (6–8, 20, 43, 56, 58, 68, 79, 81, 90, 92, 94, 96) found a significant association between receiving antianaerobic agents and VRE colonization or infection, with a pooled OR of 2.61 (95% CI, 2.02 to 3.38; $P < 0.001$).

Fluoroquinolones and other agents. Only a few clinical studies have examined in detail the association between fluoroquinolone exposure and VRE colonization. Several studies of healthy volunteers suggest that fluoroquinolones suppress anaerobic bacteria and enterococci in the normal human intestinal microflora only to a minor extent, whereas members of the family *Enterobacteriaceae* are decreased significantly (30). Conceivably, due to their relatively poor antianaerobic activity, fluoroquinolones such as ciprofloxacin do not promote high-level colonization with VRE (25). In contrast, several other studies suggest that the effects of some fluoroquinolones on fecal anaerobes may be more profound in certain patient populations, such as bone marrow transplant recipients and patients undergoing gastrointestinal surgery (50). For instance, one study reported that aerobic and anaerobic bacteria in the fecal flora were markedly suppressed during surgical prophylaxis with ciprofloxacin (14). This also may explain the effect of fluoroquinolones on VRE acquisition in severely ill patients with altered microflora. Overall, we identified 10 studies that examined the relation between exposure to fluoroquinolones and VRE colonization or infection (7, 20, 32, 36, 58, 68, 90, 94, 96, 98). When the results of these studies were combined (Cosgrove et al., 12th Annu. Sci. SHEA Meet.), a significant association between receiving fluoroquinolones and VRE colonization or infection was evident, with a pooled OR of 2.33 (95% CI, 1.5 to 3.61; $P < 0.001$).

Lastly, other agents such as aminoglycosides or aztreonam have only inconsistently been implicated as risk factors for VRE colonization or infection in hospitalized patients (68, 75).

ANTIBIOTICS AND VRE DETECTION

The main reservoir for enterococci in humans is the gastrointestinal tract. Importantly, if patients are colonized with very low numbers of VRE that are not detected by rectal swabs, emergence of these strains after patients are exposed to antibiotics might be incorrectly interpreted as true acquisition (92). Fuller et al. (35) suggested that vancomycin exposure may exert selective pressure on the gut, raising undetectable levels of preexisting VRE to detectable levels. In such a case, vancomycin administration does not "cause" VRE to develop, nor does it increase the odds that the individual patient will acquire VRE. However, it results in an apparent increase in the likelihood of VRE detection (35).

Enterococcosel enrichment broth can detect as few as one to nine colonies of enterococci per g of stool (101). The rate of VRE isolation may be seriously underestimated in the absence of a broth enrichment step (46). Several investigators (47, 48) have reported on the isolation of VRE only after broth enrichment in antibiotic-free medium, suggesting that small numbers of organisms might be missed in selective media. In another study, stool surveillance culture positivity antedated clinically apparent infection in only half of the cases (105). This may reflect the limitations of surveillance cultures in detecting small quantities of VRE.

Unfortunately, none of the above-mentioned studies ex-

plored in more details the effect of antibiotics on the exact detection threshold of VRE in different stool culturing techniques. However, Donskey et al. (24) have recently shown that the density of VRE increases shortly after antibiotic exposure and decreases over time if no other antibiotics are given. When antibiotics were discontinued, the density of VRE in stool decreased in all 19 patients from whom samples were collected 4 or more weeks later. The mean interval between the discontinuation of antibiotics and the finding of undetectable levels of VRE in stool was 17 weeks (range, 6 to 20 weeks). Another study from Van der Auwera et al. (100) showed that among 33 cancer patients who had been exposed to a glycopeptide within the 6 months prior to testing, 4 (12%) continued to have small amounts of VRE (<50 CFU/g) in their stools. In the same study from Belgium, a country where VRE carriage in the community was high until the ban of the glycopeptide avoparcin as a growth promoter for veterinary use in 1996, the investigators assessed changes in the fecal flora of 22 healthy volunteers after administration of oral glycopeptides. Their study revealed no detectable glycopeptide-resistant enterococci in the predominant flora before glycopeptide administration; however, large numbers of VRE "emerged" by the end of the study in 14 (64%) of the subjects. We believe that this observation is more likely to represent detection of latent carriage of very small amounts of VRE than new acquisition.

Finally, a recent study by Muto et al. (C. A. Muto, E. G. Cage, L. Durbin, B. Simonton, and B. M. Farr, Abstr. 9th Annu. Sci. SHEA Meet., abstr. 86, 1999) claimed that antibiotic exposure is likely a sine qua non for developing a VRE-positive perirectal culture. Of 14,335 high-risk patients cultured, 376 were positive for VRE (2.6%). Of these, 100% had received antibiotics within the previous 12 months. Eleven of 80 roommates (13.8%) who received antibiotics turned positive for VRE compared with none of the 20 roommates who did not ($P = 0.11$).

ANTIBIOTICS AND VRE TRANSMISSION

Antibiotics may increase the likelihood of transmission of VRE by their effect on patients colonized with VRE. Most importantly, fecal incontinence or diarrhea in VRE carriers may cause environmental contamination with VRE (24, 66). Unfortunately, few studies have examined the question of which classes of antibiotics are more likely to increase VRE transmission in the hospital setting.

VRE can be isolated from the stool of healthy adults and hospitalized patients during vancomycin therapy. Parenteral vancomycin treatment does not eliminate all gram-positive cocci in the oral and fecal flora and may increase the intestinal VRE load in VRE carriers (71). This may also facilitate VRE transmission, since the number of VRE in a given clinical sample is proportional to the ease with which VRE is transmitted to other body sites or to another patient (17). For instance, Beezhold et al. (4) demonstrated that while all patients with VRE bacteremia had rectal colonization with VRE, 86 and 57% also had colonization of the inguinal skin and the antecubital fossa, respectively.

Indirect evidence from ecologic studies may be cited to illustrate the association of vancomycin use and nosocomial VRE transmission. For instance, a detailed account of total

vancomycin usage in 1996 showed that much greater quantities of intravenous and oral vancomycin were used in the United States (38.2 and 3.3 kg per 1 million members of population, respectively) than in Germany (7.7 and <0.1 kg per 1 million members of population, respectively) (H. A. Kirst, D. G. Thompson, and T. I. Nicas, Letter, Antimicrob. Agents Chemother. 42:1303–1304, 1998), a country with very low rates of nosocomial VRE transmission despite a more important human VRE reservoir in the community (106).

Another recently published ecologic study (33) also showed a strong association between higher rates of vancomycin use and increased prevalence of VRE in 126 U.S. ICUs ($P < 0.001$ by linear regression analysis). However, due to its purely ecologic nature and the lack of individual-level data on antibiotic exposure, severity of illness, and LOS, this multicenter study is clearly unable to prove that the demonstrated association is causative in nature. Moreover, it remains to be elucidated if higher rates of intravenous vancomycin use are only surrogate markers for increased methicillin-resistant *Staphylococcus aureus* prevalence and, therefore, simply reflect poor hand hygiene standards in those units, also facilitating VRE cross-transmission.

Donskey et al. (24) recently showed the crucial importance of antibiotic exposure in the temporal variation of VRE fecal carriage and further demonstrated the impact of high-density intestinal VRE colonization associated with fecal incontinence on environmental contamination with VRE. These authors illustrated the risk of environmental contamination in one exemplary 69-year-old male nursing home patient who had multiple antibiotic courses with different agents, persistent carriage of the same VRE clone over 27 weeks, and microbiologically proven contamination of the patient's bedside table and bed linen. Many antibiotic classes, including fluoroquinolones, may cause antibiotic-associated diarrhea or stool incontinence in elderly or severely ill patients (19, 44). Since stool incontinence in patients with high-density VRE colonization may represent a risk factor for transmission of VRE (10), many antimicrobial agents may thus facilitate the spread of VRE.

ANTIBIOTICS AND INTESTINAL DECOLONIZATION OF VRE

Once acquired, intestinal colonization by VRE can last for years (43, 63), serving as a reservoir for potential infection of the colonized patient and for the spread of VRE to other patients. Although several attempts have been made to eradicate intestinal VRE carriage with enteral antibiotic agents, no regimen has been uniformly effective in eradicating VRE from the gastrointestinal tract (17). In a study using a mouse model in which VRE colonization was established, mice treated with a streptogramin antibiotic had recurrence of colonization 7 days after the antibiotic was given. In the same mouse model, the oral administration of vancomycin-susceptible enterococci or *Lactobacillus* spp. failed to eradicate colonization (23).

In small case series of colonized patients, combinations of novobiocin with tetracycline or bacitracin plus doxycycline showed transient effects and failed to permanently eradicate VRE from the stools of known carriers (18; M. A. Montecalvo, H. Horowitz, G. P. Wormser, K. Seiter, and C. A. Carbonaro, Letter, Antimicrob. Agents Chemother. 39:794, 1995). Only

TABLE 1. Antibiotic formulary interventions

First author (reference)	Publication yr	Setting	Intervention ^a	Outcome
Rubin (89)	1992	Pediatric oncology ward	Restriction of i.v. vancomycin	Decrease of colonization with VRE
Lam (52)	1995	Hospital	Restriction of oral vancomycin	Decrease of clinical isolates with VRE
Morris (68)	1995	Hospital	Restriction of vancomycin; no restriction of cephalosporins	No significant changes in VRE colonization or infection rates
Belliveau (5)	1996	Hospital	Restriction of vancomycin	No new VRE outbreaks but no decline in endemic VRE
Quale (85)	1996	Hospital	Restriction of vancomycin, clindamycin, and broad-spectrum cephalosporins	Decrease in fecal colonization and infections with VRE
Anglim (1)	1997	Hospital	Restriction of vancomycin; enhanced infection control measures; surveillance cultures from high-risk patients	Significant decrease in the incidence of VRE acquisition
Lai (51)	1998	Hospital	Restriction of vancomycin	No significant changes, failure of eradication
Bradley (13)	1999	Oncology unit	Restriction of ceftazidime and replacement with PIP-TZB	Significant decrease in VRE acquisition with increase after restart of ceftazidime use
Montecalvo (65)	1999	Oncology unit	Reduction in several classes of antibiotics	Decreased VRE infection and colonization rate
Smith (93)	1999	Hospital	Restriction of cephalosporins and replacement with PIP-TZB	Decline in VRE prevalence
Manzella (59)	2000	Hospital	Ceftriaxone-erythromycin versus levofloxacin treatment	Decreased VRE colonization rate
May (60)	2000	ICU	Restriction of cephalosporins and replacement with PIP-TZB	Eradication of all VRE infections
Nourse (74)	2000	Oncology unit	Restriction of cephalosporins and glycopeptides	Complete eradication of VRE infection and transmission

^a Abbreviations: i.v., intravenous; PIP-TZB, piperacillin-tazobactam.

one noncontrolled study suggested that oral therapy with doxycycline and bacitracin might be effective for longer time periods (76). In another anecdotal report, Dembry et al. (22) noted eradication of VRE colonization in two patients treated with doxycycline and rifampin in a renal unit; rectal swabs from these patients were negative at 1 and 6 months. A more recent study with better controls, however, indicated no effect beyond the 2-week interval during which the antibiotics were given (103). New approaches for achieving VRE decolonization are urgently needed. For instance, administration of probiotic agents such as *Bacillus coagulans* may represent a promising approach to intestinal VRE decolonization (27).

EXPERIMENTAL STUDIES

Experimental data substantiate the importance of antibiotics in predisposing a subject to gastrointestinal colonization with VRE (88, 107). In an experimental mouse model, antibiotic therapy with metronidazole and streptomycin resulted in overgrowth with enterococci (104). Another animal study showed that administration of vancomycin to mice permitted VRE to replace other enterococci (107). Following discontinuation of vancomycin, VRE colonization persisted in some animals at high counts.

An experimental study of 20 human volunteers (29) evaluated the ecological disturbances of oral vancomycin administration following cephalosporin administration. The concentration of vancomycin in feces after 1 week of vancomycin use was high, which correlated with the ecological disturbances noted in the vancomycin recipients. Vancomycin administra-

tion resulted in a rapid decrease in the numbers of intestinal vancomycin-susceptible *E. faecium* and *Enterococcus faecalis*, while there was a significant emergence of enterococci with decreased susceptibility to vancomycin (*Enterococcus gallinarum* and *Enterococcus casseliflavus*) (29).

In mice with established VRE colonization, as evidenced by the high density of VRE in stool, the administration of antibiotics with potent activity against anaerobes maintained a high level of colonization, whereas the administration of antibiotics with less potent antianaerobic activity did not (25). In another mouse model used by the same investigators, mice treated with ceftriaxone or ticarcillin-clavulanate developed persistently high levels of VRE carriage in stool compared to the group treated with piperacillin-tazobactam, which was protected against high-level VRE colonization (26). A consistent biological model can explain the epidemiologic findings of a strong association between extended-spectrum cephalosporin use and increased risk for VRE. As previously shown, extended-spectrum cephalosporins have minimal antienterococcal activity and may promote establishment of high-level VRE colonization (26), because the extremely high biliary concentrations of extended-spectrum cephalosporins can kill most bacteria in the upper gastrointestinal tract, except for VRE (88).

IMPACT OF ANTIBIOTIC FORMULARY INTERVENTIONS

Several investigators have studied the effect of antibiotic formulary interventions to control the problem of nosocomial VRE (Table 1). Restriction of vancomycin has been employed

the most frequently; however, results of this intervention have been inconsistent. For instance, Morris et al. (68) restricted vancomycin use at a tertiary care center with endemic VRE. During this 7-month study, intravenous vancomycin use fell by 59% and use of oral vancomycin declined by 85%. However, no significant changes were seen in rates of VRE infection or the prevalence of patients colonized with VRE. In contrast, Quale et al. (85) found that antibiotic restriction resulted in a decrease in rectal colonization and infection with VRE. These investigators altered the antibiotic formulary by restricting the use of vancomycin, cefotaxime, and clindamycin and by adding beta-lactamase inhibitors to replace broad-spectrum cephalosporins. After 6 months, the average monthly use of cefotaxime, ceftazidime, vancomycin, and clindamycin had decreased by 84, 55, 34, and 80%, respectively ($P < 0.02$). The point prevalence of fecal colonization with VRE decreased from 47 to 15% ($P < 0.001$), and the number of patients whose clinical specimens were culture positive also gradually decreased. However, this study has many methodological limitations as pointed out by Hayden (42), making it difficult to draw general conclusions from this study.

Other studies have reported similar success when cephalosporin use has been restricted or replaced by penicillin agents (93). May et al. (60) implemented an antibiotic control policy in an ICU in order to minimize cephalosporin use. Before the intervention, seven VRE infections occurred in the ICU. Following initiation of the antibiotic protocol, VRE was eradicated completely. The decrease in the VRE infection rate corresponded with a significant increase in the use of piperacillin-tazobactam and a reduction in broad-spectrum and total cephalosporin use. Another group was able to reduce the VRE acquisition rate on a hematology unit by substituting piperacillin-tazobactam for ceftazidime as a first-line treatment for patients with febrile neutropenia with no change in glycopeptide use (12, 13). The investigators measured the acquisition rate of VRE detectable by rectal swab for an initial 4-month period during which ceftazidime was used (57%), during the following 8-month period in which piperacillin-tazobactam was used (19%), and during the following 4-month period when ceftazidime was used again (36%). They found a statistically significant decrease in the probability of VRE acquisition between the first and second time periods ($P < 0.001$) and noted that clinical infections with VRE occurred only in the first and third time periods.

The theoretical mechanism of this observation is presumed to be the replacement of an antibiotic class without enterococcal activity with a class of agents active against enterococci. The MICs of extended-spectrum penicillins such as piperacillin for enterococci are much lower, and these agents achieve high levels in the bile. Thus, gastrointestinal overgrowth with VRE may be partially reduced (60), although penicillin agents such as piperacillin-tazobactam have antianaerobic activity and may potentiate the proliferation of VRE, as shown in another study (24). Confirmation by other investigators is clearly needed before the replacement of broad-spectrum cephalosporins by extended-spectrum penicillin agents can be routinely recommended for control of VRE.

Determining the relative contribution of antibiotic restriction policies to the nosocomial epidemiology of VRE remains difficult, since other infection control measures are usually

implemented at the same time as are interventions targeted at antibiotic prescribing practices. Moreover, most formulary interventions are designed as before-after studies, which may introduce bias caused by time effects. We also suspect that these interventions are subject to publication bias. However, encouraging the judicious use of certain antibiotic classes and decreasing the total volume of antibiotic use will probably affect nosocomial colonization and infection with VRE, as recently shown by Montecalvo et al. (65). In that study, enhanced infection control strategies and decreased use of all antimicrobial agents except clindamycin and amikacin reduced cross-transmission in an oncology unit with endemic VRE.

SUMMARY

VRE are important nosocomial pathogens that have spread rapidly in several countries since the first isolates were detected approximately 15 years ago. Antibiotic use has been ascribed a crucial role in the dissemination of VRE. However, findings about the effect of antibiotics on the nosocomial epidemiology of VRE have not been consistent across published studies, since multiple biases may have distorted study results (15, 41). For instance, newly detected VRE carriage after antibiotic exposure may have represented either true, nosocomial acquisition of these organisms or expansion of preexisting but previously undetected carriage of VRE in stool (Muto et al., 9th Annu. Sci. SHEA Meet.). Moreover, studies were conducted in different settings, using both case control and cohort study design. Finally, many of the publications addressing this subject had a small sample size, focused on a limited number of antimicrobial agents, or did not adjust for important confounding factors such as length of hospital stay.

Nonetheless, several useful findings may be extracted from our systematic review of the literature: (i) only a few studies have systematically examined the effect of antibiotics on the threshold of detection of VRE; (ii) in patients previously free of VRE, intravenous vancomycin use may have a limited role in facilitating new acquisition of VRE, while broad-spectrum cephalosporins or antianaerobic agents may have a more pronounced effect; (iii) many different antibiotic agents may increase VRE density in stool and may thus influence the epidemiology of VRE by increasing the likelihood of transmission; (iv) no antibiotic decolonization regimen has proven to be useful; and (v) the most-promising formulary interventions replaced broad-spectrum cephalosporins with penicillin agents, but more definitive data are needed.

POTENTIAL BIASES

The evaluation of the effect of antibiotic exposure on nosocomial VRE epidemiology is subject to major pitfalls. First, only two clinical studies (9, 96) assessed in detail the influence of "contact patterns" (i.e., individual contact episodes with VRE carriers) and "colonization pressure" (i.e., overall proportion of patients colonized with VRE in the unit), which are central to the transmission of VRE, since this nosocomial pathogen is predominantly spread by person-to-person contact. This makes the population dynamics of nosocomial VRE transmission highly nonlinear. In more general terms, when

the assumptions of independence and dynamic linearity are violated, antibiotic exposure effects that assume these statistical principles may not accurately reflect the effect of antibiotic exposures at either the individual or the population level (49). The major implication for the future design of studies about antibiotic exposure effects in nosocomial VRE epidemiology is that individual contact episodes with VRE carriers or the overall colonization pressure in a defined population should be measured (9). Mathematical models can be used to predict the expected decrease in VRE transmission after the implementation of certain interventions in an individual hospital. For instance, Austin et al. (2, 3) utilized mathematical modeling to address the complex interactions between VRE transmission and acquisition, rates of colonization and infection, and the effects of infection control measures and antibiotic restriction policies.

Second, most previous studies did not examine in detail the dose dependency, time effects, and interactions between different antibiotic agents. Duration of antibiotic treatment and potential posttreatment effects also influence intestinal VRE carriage (79). Interactions between different agents should be investigated in more detail in future studies, as suggested by Tornieporth et al. (97).

Third, most studies, particularly those performed in the early 1990s, do not prove de novo acquisition of VRE in their study subjects, since they often do not demonstrate that VRE-positive patients were truly VRE negative at study entry. Studies that are done retrospectively are more likely to have this problem and should be examined with caution regarding this issue. Prospective studies that examined patients whose initial VRE cultures were negative but who subsequently became VRE positive during follow-up may better address this problem. However, prospective studies using serial surveillance cultures have small sample size and not enough power to examine antibiotic exposures as a risk factor for de novo acquisition.

Finally, many articles about the association between specific antibiotic agents and nosocomial VRE occurrence have methodological deficiencies that may limit their validity. For instance, the reported association between vancomycin use and individual risk for nosocomial VRE acquisition may be distorted by the selection of inappropriate control groups (i.e., patients with infections due to vancomycin-sensitive enterococci), lack of control for differences in duration of hospital stay between patients and controls, and publication bias (15, 41).

In particular, ecologic studies such as the recently published study by Fridkin et al. (33) are prone to methodological shortcomings, since the analysis of aggregated data may be limited by "ecologic bias," which is the failure of group-level effect estimates to reflect the presence or absence of a biologic effect at the individual-patient level (37). This bias is due to the fact that, unlike individual-level studies, ecologic studies do not link individual outcome events to individual exposure histories. As recently shown (39), group- and individual-patient-level analyses of antibiotic usage-versus-susceptibility relations may give divergent results. Thus, multicenter studies about VRE occurrence should include individual-patient-level data to more fully elucidate the relation between antibiotic exposure and VRE rates (39).

IMPLICATIONS

Our review has several implications for physicians and infection control practitioners. Gastrointestinal colonization with VRE may occur in extremely high titers in the feces (107). This explains why the organism readily contaminates the environment surrounding infected patients, especially those with antibiotic-related diarrhea, causing spread to other patients (10, 65). Consequently, strictly enforced infection control measures are necessary to prevent the spread of VRE. Because extensive environmental contamination may occur when affected patients develop diarrhea, barrier precautions, including the use of both gowns and gloves, must be implemented as soon as these pathogens are encountered (10). Moreover, more research is needed to early identify patients with a high risk of VRE transmission in the hospital setting.

Although vancomycin use may have been critical in the initial emergence of VRE, the unbiased analysis of clinical studies using individual-patient-level data for the evaluation of the association between vancomycin and VRE found minimal evidence that this antibiotic is associated with VRE acquisition in previously VRE-free individuals. Most of these studies included predominantly patients who received intravenous vancomycin, which is excreted renally with minimal concentrations in feces. In contrast, oral vancomycin use achieves much higher drug levels intraluminally and may promote overgrowth by glycopeptide-resistant species (A. D. Luber, R. A. Jacobs, M. Jordan, and B. J. Guglielmo, *Letter, J. Infect. Dis.* **173**:1292–1294, 1996). Thus, oral vancomycin use may have been a risk factor for the emergence of VRE colonization, at least in the early phase of the epidemic (34, 88). In fact, in the 1980s, orally administered vancomycin was a widely used treatment for *C. difficile* colitis, until recommendations were established discouraging the use of this agent for the primary treatment of antibiotic-associated diarrhea.

As shown in several clinical studies (28, 92), broad-spectrum cephalosporins may offer greater selective advantage in settings with endemic VRE. The reduction of gastrointestinal anaerobes in particular may create a survival advantage for VRE. In contrast, some evidence suggests that the use of penicillin agents such as ampicillin-sulbactam, piperacillin, and piperacillin-tazobactam may be protective against the spread of VRE in the hospital setting (28, 102). However, further research is needed to determine the optimal method of antibiotic control in order to decrease VRE prevalence.

CONCLUSIONS

In summary, antibiotics are able to influence nosocomial VRE epidemiology at different levels. In a patient initially free of VRE, antibiotics may decrease resistance against VRE colonization in the gastrointestinal tract and may increase susceptibility to becoming colonized with this microorganism. In a patient already colonized with VRE, antibiotic exposure may inhibit other bacteria and enhance bacterial overgrowth with VRE in the gut. This may increase the likelihood that VRE might be detected in screening cultures. Antibiotic exposure may also increase the potential for transmission by causing stool incontinence, which may increase the risk of environmental contamination with VRE. Finally, antibiotic exposure may

decrease the intestinal bacterial burden if the agent is active against the colonizing VRE strain. In broader terms, the effect of an antibiotic agent on nosocomial VRE epidemiology depends on the carriage state of the individual patient or patients in close contact and the interaction of antibiotic agents with the competing intestinal microflora of the concerned individual.

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REFERENCES

- Anglim, A. M., B. Klym, K. E. Byers, W. M. Scheld, and B. M. Farr. 1997. Effect of a vancomycin restriction policy on ordering practices during an outbreak of vancomycin-resistant *Enterococcus faecium*. *Arch. Intern. Med.* **157**:1132–1136.
- Austin, D. J., and R. M. Anderson. 1999. Transmission dynamics of epidemic methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in England and Wales. *J. Infect. Dis.* **179**:883–891.
- Austin, D. J., M. J. Bonten, R. A. Weinstein, S. Slaughter, and R. M. Anderson. 1999. Vancomycin-resistant enterococci in intensive-care hospital settings: transmission dynamics, persistence, and the impact of infection control programs. *Proc. Natl. Acad. Sci. USA* **96**:6908–6913.
- Beezhold, D. W., S. Slaughter, M. K. Hayden, M. Matushek, C. Nathan, G. M. Trenholme, and R. A. Weinstein. 1997. Skin colonization with vancomycin-resistant enterococci among hospitalized patients with bacteremia. *Clin. Infect. Dis.* **24**:704–706.
- Belliveau, P. P., A. L. Rothman, and C. E. Maday. 1996. Limiting vancomycin use to combat vancomycin-resistant *Enterococcus faecium*. *Am. J. Health Syst. Pharm.* **53**:1570–1575.
- Beltrami, E. M., D. A. Singer, L. Fish, K. Manning, S. Young, S. N. Banerjee, R. Baker, and W. R. Jarvis. 2000. Risk factors for acquisition of vancomycin-resistant enterococci among patients on a renal ward during a community hospital outbreak. *Am. J. Infect. Control* **28**:282–285.
- Bhavnani, S. M., J. A. Drake, A. Forrest, J. A. Deinhart, R. N. Jones, D. J. Biedenbach, and C. H. Ballow. 2000. A nationwide, multicenter, case-control study comparing risk factors, treatment, and outcome for vancomycin-resistant and -susceptible enterococcal bacteremia. *Diagn. Microbiol. Infect. Dis.* **36**:145–158.
- Bonten, M. J., M. K. Hayden, C. Nathan, J. van Voorhis, M. Matushek, S. Slaughter, T. Rice, and R. A. Weinstein. 1996. Epidemiology of colonisation of patients and environment with vancomycin-resistant enterococci. *Lancet* **348**:1615–1619.
- Bonten, M. J., S. Slaughter, A. W. Ambergen, M. K. Hayden, J. van Voorhis, C. Nathan, and R. A. Weinstein. 1998. The role of "colonization pressure" in the spread of vancomycin-resistant enterococci: an important infection control variable. *Arch. Intern. Med.* **158**:1127–1132.
- Boyce, J. M., S. M. Opal, J. W. Chow, M. J. Zervos, G. Potter-Bynoe, C. B. Sherman, R. L. Romulo, S. Fortna, and A. A. Medeiros. 1994. Outbreak of multidrug-resistant *Enterococcus faecium* with transferable *vanB* class vancomycin resistance. *J. Clin. Microbiol.* **32**:1148–1153.
- Boyle, J. F., S. A. Soumakis, A. Rendo, J. A. Herrington, D. G. Gianarkis, B. E. Thurberg, and B. G. Painter. 1993. Epidemiologic analysis and genotypic characterization of a nosocomial outbreak of vancomycin-resistant enterococci. *J. Clin. Microbiol.* **31**:1280–1285.
- Bradley, S. J. 2000. Control of glycopeptide-resistant enterococci in an oncology unit. *Pharmacotherapy* **20**:203–212.
- Bradley, S. J., A. L. Wilson, M. C. Allen, H. A. Sher, A. H. Goldstone, and G. M. Scott. 1999. The control of hyperendemic glycopeptide-resistant *Enterococcus* spp. on a haematology unit by changing antibiotic usage. *J. Antimicrob. Chemother.* **43**:261–266.
- Brismar, B., C. Edlund, A. S. Malmberg, and C. E. Nord. 1990. Ciprofloxacin concentrations and impact of the colon microflora in patients undergoing colorectal surgery. *Antimicrob. Agents Chemother.* **34**:481–483.
- Carmeli, Y., M. H. Samore, and C. Huskins. 1999. The association between antecedent vancomycin treatment and hospital-acquired vancomycin-resistant enterococci: a meta-analysis. *Arch. Intern. Med.* **159**:2461–2468.
- Centers for Disease Control and Prevention. 2000. National nosocomial infections surveillance (NNIS) system report, data summary from January 1992–April 2000. *Am. J. Infect. Control* **28**:429–448.
- Cetinkaya, Y., P. Falk, and C. G. Mayhall. 2000. Vancomycin-resistant enterococci. *Clin. Microbiol. Rev.* **13**:686–707.
- Chia, J. K., M. M. Nakata, S. S. Park, R. P. Lewis, and B. McKee. 1995. Use of bacitracin therapy for infection due to vancomycin-resistant *Enterococcus faecium*. *Clin. Infect. Dis.* **21**:1520.
- Crabtree, T. D., S. J. Pelletier, T. G. Gleason, T. L. Pruett, and R. G. Sawyer. 1999. Clinical characteristics and antibiotic utilization in surgical patients with *Clostridium difficile*-associated diarrhea. *Am. Surg.* **65**:507–511.
- D'Agata, E. M., W. K. Green, G. Schulman, H. Li, Y. W. Tang, and W. Schaffner. 2001. Vancomycin-resistant enterococci among chronic hemodialysis patients: a prospective study of acquisition. *Clin. Infect. Dis.* **32**:23–29.
- Dahms, R. A., E. M. Johnson, C. L. Statz, J. T. Lee, D. L. Dunn, and G. J. Beilman. 1998. Third-generation cephalosporins and vancomycin as risk factors for postoperative vancomycin-resistant enterococcus infection. *Arch. Surg.* **133**:1343–1346.
- Dembry, L. M., K. Uzokwe, and M. J. Zervos. 1996. Control of endemic glycopeptide-resistant enterococci. *Infect. Control Hosp. Epidemiol.* **17**:286–292.
- Dever, L. L., and S. Handwerger. 1996. Persistence of vancomycin-resistant *Enterococcus faecium* gastrointestinal tract colonization in antibiotic-treated mice. *Microb. Drug Resist.* **2**:415–421.
- Donskey, C. J., T. K. Chowdhry, M. T. Hecker, C. K. Hoen, J. A. Hanrahan, A. M. Hujer, R. A. Hutton-Thomas, C. C. Whalen, R. A. Bonomo, and L. B. Rice. 2000. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *N. Engl. J. Med.* **343**:1925–1932.
- Donskey, C. J., J. A. Hanrahan, R. A. Hutton, and L. B. Rice. 1999. Effect of parenteral antibiotic administration on persistence of vancomycin-resistant *Enterococcus faecium* in the mouse gastrointestinal tract. *J. Infect. Dis.* **180**:384–390.
- Donskey, C. J., J. A. Hanrahan, R. A. Hutton, and L. B. Rice. 2000. Effect of parenteral antibiotic administration on the establishment of colonization with vancomycin-resistant *Enterococcus faecium* in the mouse gastrointestinal tract. *J. Infect. Dis.* **181**:1830–1833.
- Donskey, C. J., C. K. Hoen, S. M. Das, S. Farmer, M. Dery, and R. A. Bonomo. 2001. Effect of oral *Bacillus coagulans* administration on the density of vancomycin-resistant enterococci in the stool of colonized mice. *Lett. Appl. Microbiol.* **33**:84–88.
- Donskey, C. J., J. R. Schreiber, M. R. Jacobs, R. Shekar, R. A. Salata, S. Gordon, C. C. Whalen, F. Smith, L. B. Rice, et al. 1999. A polyclonal outbreak of predominantly VanB vancomycin-resistant enterococci in northeast Ohio. *Clin. Infect. Dis.* **29**:573–579.
- Edlund, C., L. Barkholt, B. Olsson-Liljequist, and C. E. Nord. 1997. Effect of vancomycin on intestinal flora of patients who previously received antimicrobial therapy. *Clin. Infect. Dis.* **25**:729–732.
- Edlund, C., and C. E. Nord. 1999. Effect of quinolones on intestinal ecology. *Drugs* **58**(Suppl. 2):65–70.
- Edmond, M. B., J. F. Ober, D. L. Weinbaum, M. A. Pfaller, T. Hwang, M. D. Sanford, and R. P. Wenzel. 1995. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. *Clin. Infect. Dis.* **20**:1126–1133.
- Falk, P. S., J. Winnike, C. Woodmansee, M. Desai, and C. G. Mayhall. 2000. Outbreak of vancomycin-resistant enterococci in a burn unit. *Infect. Control Hosp. Epidemiol.* **21**:575–582.
- Fridkin, S. K., J. R. Edwards, J. M. Courval, H. Hill, F. C. Tenover, R. Lawton, R. P. Gaynes, and J. E. McGowan. 2001. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. *Ann. Intern. Med.* **135**:175–183.
- Frieden, T. R., S. S. Munsiff, D. E. Low, B. M. Willey, G. Williams, Y. Faur, W. Eisner, S. Warren, and B. Kreiswirth. 1993. Emergence of vancomycin-resistant enterococci in New York City. *Lancet* **342**:76–79.
- Fuller, R. E., L. J. Harrell, F. T. Meredith, D. J. Sexton, and L. G. Colvin. 1998. Vancomycin-resistant enterococci: risk related to the use of intravenous vancomycin in a university hospital. *Infect. Control Hosp. Epidemiol.* **19**:821–823.
- Gordts, B., H. Van Landuyt, M. Ieven, P. Vandamme, and H. Goossens. 1995. Vancomycin-resistant enterococci colonizing the intestinal tracts of hospitalized patients. *J. Clin. Microbiol.* **33**:2842–2846.
- Greenland, S. 1992. Divergent biases in ecologic and individual-level studies. *Stat. Med.* **11**:1209–1223.
- Handwerger, S., B. Raucher, D. Altarac, J. Monka, S. Marchione, K. V. Singh, B. E. Murray, J. Wolff, and B. Walters. 1993. Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin, and gentamicin. *Clin. Infect. Dis.* **16**:750–755.
- Harbarth, S., A. Harris, Y. Carmeli, and M. H. Samore. 2001. Parallel analysis of individual and aggregated data on antibiotic exposure and resistance in gram-negative bacilli. *Clin. Infect. Dis.* **33**:1462–1468.
- Harbarth, S., M. H. Samore, D. Lichtenberg, and Y. Carmeli. 2000. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation* **101**:2916–2921.
- Harris, A. D., T. B. Karchmer, Y. Carmeli, and M. H. Samore. 2001. Methodological principles of case-control studies that analyzed risk factors for antibiotic resistance: a systematic review. *Clin. Infect. Dis.* **32**:1055–1061.

42. Hayden, M. K. 2000. Insights into the epidemiology and control of infection with vancomycin-resistant enterococci. *Clin. Infect. Dis.* **31**:1058–1065.
43. Henning, K. J., H. Delencastre, J. Eagan, N. Boone, A. Brown, M. Chung, N. Wollner, and D. Armstrong. 1996. Vancomycin-resistant *Enterococcus faecium* on a pediatric oncology ward: duration of stool shedding and incidence of clinical infection. *Pediatr. Infect. Dis. J.* **15**:848–854.
44. Hooker, K. D., and J. T. DiPiro. 1988. Effect of antimicrobial therapy on bowel flora. *Clin. Pharmacokinet.* **7**:878–888.
45. Hwang, Y. S., B. G. Brinton, R. B. Leonard, S. R. Blue, M. L. Woods, and K. C. Carroll. 1998. Investigation of an outbreak of vancomycin-resistant *Enterococcus faecium* in a low prevalence university hospital. *J. Invest. Med.* **46**:435–443.
46. Ieven, M., E. Vercauteren, P. Descheemaeker, F. van Laer, and H. Goossens. 1999. Comparison of direct plating and broth enrichment culture for the detection of intestinal colonization by glycopeptide-resistant enterococci among hospitalized patients. *J. Clin. Microbiol.* **37**:1436–1440.
47. Jordens, J. Z., J. Bates, and D. T. Griffiths. 1994. Faecal carriage and nosocomial spread of vancomycin-resistant *Enterococcus faecium*. *J. Antimicrob. Chemother.* **34**:515–528.
48. Klare, I., H. Heier, H. Claus, R. Reissbrodt, and W. Witte. 1995. vanA-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry. *FEMS Microbiol. Lett.* **125**:165–172.
49. Koopman, J. S., and I. M. Longini, Jr. 1994. The ecological effects of individual exposures and nonlinear disease dynamics in populations. *Am. J. Public Health* **84**:836–842.
50. Korten, V., and B. E. Murray. 1993. Impact of the fluoroquinolones on gastrointestinal flora. *Drugs* **45**(Suppl. 3):125–133.
51. Lai, K. K., A. L. Kelley, Z. S. Melvin, P. P. Belliveau, and S. A. Fontecchio. 1998. Failure to eradicate vancomycin-resistant enterococci in a university hospital and the cost of barrier precautions. *Infect. Control Hosp. Epidemiol.* **19**:647–652.
52. Lam, S., C. Singer, V. Tucci, V. H. Morthland, M. A. Pfaller, and H. D. Isenberg. 1995. The challenge of vancomycin-resistant enterococci: a clinical and epidemiologic study. *Am. J. Infect. Control* **23**:170–180.
53. Lautenbach, E., W. B. Bilker, and P. J. Brennan. 1999. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. *Infect. Control Hosp. Epidemiol.* **20**:318–323.
54. Leclercq, R., E. Derlot, J. Duval, and P. Courvalin. 1988. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. *N. Engl. J. Med.* **319**:157–161.
55. Livornese, L. L., Jr., S. Dias, C. Samel, B. Romanowski, S. Taylor, P. May, P. Pitsakis, G. Woods, D. Kaye, M. E. Levison, et al. 1992. Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. *Ann. Intern. Med.* **117**:112–116.
56. Loeb, M., S. Salama, M. Armstrong-Evans, G. Capretta, and J. Olde. 1999. A case-control study to detect modifiable risk factors for colonization with vancomycin-resistant enterococci. *Infect. Control Hosp. Epidemiol.* **20**:760–763.
57. Low, D. E., N. Keller, A. Barth, and R. N. Jones. 2001. Clinical prevalence, antimicrobial susceptibility, and geographic resistance patterns of enterococci: results from the sentry antimicrobial surveillance program, 1997–1999. *Clin. Infect. Dis.* **32**(Suppl. 2):S133–S145.
58. Lucas, G. M., N. Lechtzin, D. W. Puryear, L. L. Yau, C. W. Flexner, and R. D. Moore. 1998. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: comparison of clinical features and outcomes. *Clin. Infect. Dis.* **26**:1127–1133.
59. Manzella, J., R. Benenson, G. Pellerin, J. Kellogg, T. Bell, M. Robertson, and D. Pope. 2000. Choice of antibiotic and risk of colonization with vancomycin-resistant *Enterococcus* among patients admitted for treatment of community-acquired pneumonia. *Infect. Control Hosp. Epidemiol.* **21**:789–791.
60. May, A. K., S. M. Melton, G. McGwin, J. M. Cross, S. A. Moser, and L. W. Rue. 2000. Reduction of vancomycin-resistant enterococcal infections by limitation of broad-spectrum cephalosporin use in a trauma and burn intensive care unit. *Shock* **14**:259–264.
61. McManus, A. T., C. W. Goodwin, and B. A. Pruitt, Jr. 1998. Observations on the risk of resistance with the extended use of vancomycin. *Arch. Surg.* **133**:1207–1211.
62. Moellering, R. C., Jr. 1998. Vancomycin-resistant enterococci. *Clin. Infect. Dis.* **26**:1196–1199.
63. Montecalvo, M. A., H. de Lencastre, M. Carraher, C. Gedris, M. Chung, K. VanHorn, and G. P. Wormser. 1995. Natural history of colonization with vancomycin-resistant *Enterococcus faecium*. *Infect. Control Hosp. Epidemiol.* **16**:680–685.
64. Montecalvo, M. A., H. Horowitz, C. Gedris, C. Carbonaro, F. C. Tenover, A. Issah, P. Cook, and G. P. Wormser. 1994. Outbreak of vancomycin-, ampicillin-, and aminoglycoside-resistant *Enterococcus faecium* bacteremia in an adult oncology unit. *Antimicrob. Agents Chemother.* **38**:1363–1367.
65. Montecalvo, M. A., W. R. Jarvis, J. Uman, D. K. Shay, C. Petrullo, K. Rodney, C. Gedris, H. W. Horowitz, and G. P. Wormser. 1999. Infection-control measures reduce transmission of vancomycin-resistant enterococci in an endemic setting. *Ann. Intern. Med.* **131**:269–272.
66. Montecalvo, M. A., D. K. Shay, C. Gedris, C. Petrullo, J. Uman, K. Rodney, W. R. Jarvis, and G. P. Wormser. 1997. A semiquantitative analysis of the fecal flora of patients with vancomycin-resistant enterococci: colonized patients pose an infection control risk. *Clin. Infect. Dis.* **25**:929–930.
67. Moreno, F., P. Grota, C. Crisp, K. Magnon, G. P. Melcher, J. H. Jorgensen, and J. E. Patterson. 1995. Clinical and molecular epidemiology of vancomycin-resistant *Enterococcus faecium* during its emergence in a city in southern Texas. *Clin. Infect. Dis.* **21**:1234–1237.
68. Morris, J. G., Jr., D. K. Shay, J. N. Hebden, R. J. McCarter, Jr., B. E. Perdue, W. Jarvis, J. A. Johnson, T. C. Dowling, L. B. Polish, and R. S. Schwalbe. 1995. Enterococci resistant to multiple antimicrobial agents, including vancomycin. Establishment of endemicity in a university medical center. *Ann. Intern. Med.* **123**:250–259.
69. Moulin, F., S. Dumontier, P. Saulnier, E. Chachaty, C. Loubeyre, L. Bruguieres, and A. Andremon. 1996. Surveillance of intestinal colonization and of infection by vancomycin-resistant enterococci in hospitalized cancer patients. *Clin. Microbiol. Infect.* **2**:192–199.
70. Murray, B. E. 2000. Vancomycin-resistant enterococcal infections. *N. Engl. J. Med.* **342**:710–721.
71. Murray, B. E. 1995. What can we do about vancomycin-resistant enterococci? *Clin. Infect. Dis.* **20**:1134–1136.
72. Newell, K. A., J. M. Millis, P. M. Arnow, D. S. Bruce, E. S. Woodle, D. C. Cronin, G. E. Loss, H. Grewal, T. Lissos, T. Schiano, J. Mead, and J. R. Thistlethwaite, Jr. 1998. Incidence and outcome of infection by vancomycin-resistant *Enterococcus* following orthotopic liver transplantation. *Transplantation* **65**:439–442.
73. Noskin, G. A., V. Stosor, I. Cooper, and L. R. Peterson. 1995. Recovery of vancomycin-resistant enterococci on fingertips and environmental surfaces. *Infect. Control Hosp. Epidemiol.* **16**:577–581.
74. Nourse, C., C. Byrne, H. Murphy, M. E. Kaufmann, A. Clarke, and K. Butler. 2000. Eradication of vancomycin resistant *Enterococcus faecium* from a paediatric oncology unit and prevalence of colonization in hospitalized and community-based children. *Epidemiol. Infect.* **124**:53–59.
75. Nourse, C., H. Murphy, C. Byrne, A. O'Meara, F. Breatnach, M. Kaufmann, A. Clarke, and K. Butler. 1998. Control of a nosocomial outbreak of vancomycin-resistant *Enterococcus faecium* in a paediatric oncology unit: risk factors for colonisation. *Eur. J. Pediatr.* **157**:20–27.
76. O'Donovan, C. A., P. Fan-Havard, F. T. Tecson-Tumang, S. M. Smith, and R. H. Eng. 1994. Enteric eradication of vancomycin-resistant *Enterococcus faecium* with oral bacitracin. *Diagn. Microbiol. Infect. Dis.* **18**:105–109.
77. Orloff, S. L., A. M. Busch, A. J. Olyaei, C. L. Corless, K. G. Benner, K. D. Flora, H. R. Rosen, and J. M. Rabkin. 1999. Vancomycin-resistant *Enterococcus* in liver transplant patients. *Am. J. Surg.* **177**:418–422.
78. Ostrowsky, B. E., W. E. Trick, A. H. Sohn, S. B. Quirk, S. Holt, L. A. Carson, B. C. Hill, M. J. Arduino, M. J. Kuehnert, and W. R. Jarvis. 2001. Control of vancomycin-resistant *Enterococcus* in health care facilities in a region. *N. Engl. J. Med.* **344**:1427–1433.
79. Ostrowsky, B. E., L. Venkataraman, E. M. D'Agata, H. S. Gold, P. C. DeGirolami, and M. H. Samore. 1999. Vancomycin-resistant enterococci in intensive care units: high frequency of stool carriage during a non-outbreak period. *Arch. Intern. Med.* **159**:1467–1472.
80. Papanicolaou, G. A., B. R. Meyers, J. Meyers, M. H. Mendelson, W. Lou, S. Emre, P. Sheiner, and C. Miller. 1996. Nosocomial infections with vancomycin-resistant *Enterococcus faecium* in liver transplant recipients: risk factors for acquisition and mortality. *Clin. Infect. Dis.* **23**:760–766.
81. Pegues, D. A., C. F. Pegues, P. L. Hibberd, D. S. Ford, and D. C. Hooper. 1997. Emergence and dissemination of a highly vancomycin-resistant *vanA* strain of *Enterococcus faecium* at a large teaching hospital. *J. Clin. Microbiol.* **35**:1565–1570.
82. Peset, V., P. Tallon, C. Sola, E. Sanchez, A. Sarrion, C. Perez-Belles, A. Vindel, E. Canton, and M. Gobernado. 2000. Epidemiological, microbiological, clinical, and prognostic factors of bacteremia caused by high-level vancomycin-resistant *Enterococcus* species. *Eur. J. Clin. Microbiol. Infect. Dis.* **19**:742–749.
83. Pfundstein, J., M. C. Roghmann, R. S. Schwalbe, S. Q. Qaiyumi, R. J. McCarter, Jr., S. Keay, E. Schweitzer, S. T. Bartlett, J. G. Morris, Jr., and D. W. Oldach. 1999. A randomized trial of surgical antimicrobial prophylaxis with and without vancomycin in organ transplant patients. *Clin. Transplant.* **13**:245–252.
84. Quale, J., D. Landman, E. Atwood, B. Kreiswirth, B. M. Willey, V. Ditore, M. Zaman, K. Patel, G. Saurina, W. Huang, E. Oydna, and S. Burney. 1996. Experience with a hospital-wide outbreak of vancomycin-resistant enterococci. *Am. J. Infect. Control* **24**:372–379.
85. Quale, J., D. Landman, G. Saurina, E. Atwood, V. DiTore, and K. Patel. 1996. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. *Clin. Infect. Dis.* **23**:1020–1025.
86. Rao, G. G., F. Ojo, and D. Kolokithas. 1997. Vancomycin-resistant gram-positive cocci: risk factors for faecal carriage. *J. Hosp. Infect.* **35**:63–69.
87. Reacher, M. H., A. Shah, D. M. Livermore, M. C. Wale, C. Graham, A. P. Johnson, H. Heine, M. A. Monnickendam, K. F. Barker, D. James, and R. C. George. 2000. Bacteraemia and antibiotic resistance of its pathogens

- reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* **320**:213–216.
88. Rice, L. B. 2001. Emergence of vancomycin-resistant enterococci. *Emerg Infect. Dis.* **7**:183–187.
89. Rubin, L. G., V. Tucci, E. Cercenado, G. Eliopoulos, and H. D. Isenberg. 1992. Vancomycin-resistant *Enterococcus faecium* in hospitalized children. *Infect. Control Hosp. Epidemiol.* **13**:700–705.
90. Shay, D. K., S. A. Maloney, M. Montecalvo, S. Banerjee, G. P. Wormser, M. J. Arduino, L. A. Bland, and W. R. Jarvis. 1995. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *J. Infect. Dis.* **172**:993–1000.
91. Singh-Naz, N., A. Sleemi, A. Pikis, K. M. Patel, and J. M. Campos. 1999. Vancomycin-resistant *Enterococcus faecium* colonization in children. *J. Clin. Microbiol.* **37**:413–416.
92. Slaughter, S., M. K. Hayden, C. Nathan, T. C. Hu, T. Rice, J. Van Voorhis, M. Matushek, C. Franklin, and R. A. Weinstein. 1996. A comparison of the effect of universal use of gloves and gowns with that of glove use alone on acquisition of vancomycin-resistant enterococci in a medical intensive care unit. *Ann. Intern. Med.* **125**:448–456.
93. Smith, D. W. 1999. Decreased antimicrobial resistance after changes in antibiotic use. *Pharmacotherapy* **19**:129S–132S, 133S–137S.
94. Stosor, V., L. R. Peterson, M. Postelnick, and G. A. Noskin. 1998. Enterococcus faecium bacteremia: does vancomycin resistance make a difference? *Arch. Intern. Med.* **158**:522–527.
95. Suppola, J. P., L. Volin, V. V. Valtonen, and M. Vaara. 1996. Overgrowth of *Enterococcus faecium* in the feces of patients with hematologic malignancies. *Clin. Infect. Dis.* **23**:694–697.
96. Tokars, J. I., S. Satake, D. Rimland, L. Carson, E. R. Miller, E. Killum, R. L. Sinkowitz-Cochran, M. J. Arduino, F. C. Tenover, B. Marston, and W. R. Jarvis. 1999. The prevalence of colonization with vancomycin-resistant *Enterococcus* at a Veterans' Affairs institution. *Infect. Control Hosp. Epidemiol.* **20**:171–175.
97. Tornieporth, N. G., R. B. Roberts, J. John, A. Hafner, and L. W. Riley. 1996. Risk factors associated with vancomycin-resistant *Enterococcus faecium* infection or colonization in 145 matched case patients and control patients. *Clin. Infect. Dis.* **23**:767–772.
98. Toye, B., J. Shymanski, M. Bobrowska, W. Woods, and K. Ramotar. 1997. Clinical and epidemiological significance of enterococci intrinsically resistant to vancomycin (possessing the *vanC* genotype). *J. Clin. Microbiol.* **35**:3166–3170.
99. Trabulsi, A., A. M. Glover, S. F. Reising, and C. D. Christie. 1998. Absence of rectal colonization with vancomycin-resistant enterococci among high-risk pediatric patients. *Infect. Control Hosp. Epidemiol.* **19**:109–112.
100. Van der Auwera, P., N. Pensart, V. Korten, B. E. Murray, and R. Leclercq. 1996. Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. *J. Infect. Dis.* **173**:1129–1136.
101. van Horn, K. G., C. A. Gedris, and K. M. Rodney. 1996. Selective isolation of vancomycin-resistant enterococci. *J. Clin. Microbiol.* **34**:924–927.
102. Wade, J. J. 1995. The emergence of *Enterococcus faecium* resistant to glycopeptides and other standard agents—a preliminary report. *J. Hosp. Infect.* **30**(Suppl.):483–493.
103. Weinstein, M. R., H. Dedier, J. Brunton, I. Campbell, and J. M. Conly. 1999. Lack of efficacy of oral bacitracin plus doxycycline for the eradication of stool colonization with vancomycin-resistant *Enterococcus faecium*. *Clin. Infect. Dis.* **29**:361–366.
104. Wells, C. L., R. P. Jechorek, M. A. Maddaus, and R. L. Simmons. 1988. Effects of clindamycin and metronidazole on the intestinal colonization and translocation of enterococci in mice. *Antimicrob. Agents Chemother.* **32**:1769–1775.
105. Wells, C. L., B. A. Juni, S. B. Cameron, K. R. Mason, D. L. Dunn, P. Ferrieri, and F. S. Rhame. 1995. Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. *Clin. Infect. Dis.* **21**:45–50.
106. Wendt, C., C. Krause, L. U. Xander, D. Löffler, and H. Floss. 1999. Prevalence of colonization with vancomycin-resistant enterococci in various population groups in Berlin, Germany. *J. Hosp. Infect.* **42**:193–200.
107. Whitman, M. S., P. G. Pitsakis, E. DeJesus, A. J. Osborne, M. E. Levison, and C. C. Johnson. 1996. Gastrointestinal tract colonization with vancomycin-resistant *Enterococcus faecium* in an animal model. *Antimicrob. Agents Chemother.* **40**:1526–1530.
108. Willems, R. J., W. Homan, J. Top, M. van Santen-Verheul, D. Tribe, X. Manziros, C. Gaillard, C. M. Vandenbroucke-Grauls, E. M. Mascini, E. van Kregten, J. D. van Embden, and M. J. Bonten. 2001. Variant *esp* gene as a marker of a distinct genetic lineage of vancomycin-resistant *Enterococcus faecium* spreading in hospitals. *Lancet* **357**:853–855.